REMARKS/ARGUMENTS

Overview of listing of claims:

Claims 1-13 and 17-20 remain in the application. Claims 14-16 have been cancelled.

Claims 1-4, 9-13, 17, and 19-20 have been currently amended by striking through deleted matter and underlining inserted matter.

Overview of currently amended claims:

Claims 1-4 have been amended in response to the Examiner's 35 U.S.C. 112 rejection as discussed more fully below.

Claim 4 has been amended at line 4 to correct a typographical error of "urogenital" to "urogenitally".

Claim 9 has been amended to correct inconsistency with the specification as filed at p. 11, lines 20-22.

Claim 10 has been amended to include benzoic acid derivatives. The amendment is supported by the specification as filed at p. 12, lines 9-10.

Claim 11 has been amended to include polysorbate. The amendment is supported by the specification as filed at p. 11, line 10.

Claim 12 has been amended to correct inconsistency with the specification as filed at p. 11, lines 22-22. Claim 12 also has been amended in response to the Examiner's 35 U.S.C. 112 rejection as discussed more fully below. Claim 12 also has been amended at line 2 to correct a typographical error of "urogenital" to "urogenitally", and at line 6 to correct a typographical error of "anorectally" to "anorcctal".

Claim 13 has been amended to correct inconsistency with the specification as filed at p. 11, lines 22-22 and p. 12, lines 2-3. Claim 13 also has been amended in response to the Examiner's 35 U.S.C. 112 rejection as discussed more fully below.

Claim 17 has been amended at line 10 to correct a typographical error of "combination" to "combinations".

Claim 19 has been amended to correct inconsistency with the specification as filed at p. 12, lines 2-3.

Claim 20 has been amended to eliminate dependency upon previously cancelled claim 14 and to correct inconsistency with the specification as filed at p. 11, lines 20-22.

Discussion of rejections maintained (paragraphs 11-36):

Claims 1-13, 17-20 rejected under 35 U.S.C. 112, first paragraph because the specification does not reasonably provide enablement for any and all antigens to be used in a suppository based delivery system for the stimulation of a protective immune response that prevents infection – paragraphs 11 and 19-24 of paper number 13.

Claims 1, 2, 3, 13, and 17 have been amended to delete reference to "other antigenic determinants". Claims 1 (line 6), 2 (line 5), 3 (line 6), 13 (line 6), and 17 (lines 6-7) have been amended by deleting "consists of" and inserting therefor "comprises" at the noted lines. Support for the latter amendments is provided in the specification as filed at p. 5 (lines 6-10), p. 7 (lines 9-14), and p. 10 (lines 18-22).

Applicants believe that these amendments overcome the rejection, and reconsideration is requested.

Claims 1-3, 13 rejected under 35 U.S.C. 112, second paragraph for reciting the phrase "other antigenic determinants or combinations thereof" in light of "other antigenic

determinants" not having been defined or clarified – paragraphs 12 and 25-26 of paper number 13.

Claims 1, 2, 3, 13, and 17 have been amended to delete reference to "other antigenic determinants".

Applicants believe that these amendments overcome the rejection, and reconsideration is requested.

Claim 4 rejected under 35 U.S.C. 112, second paragraph for reciting the phrase "is generated from known genetic information" in light of the genetic material that is vaccine information not having been clearly defined in the claims – paragraphs 13 and 27-28 of paper number 13.

Claim 4 has been amended to delete "or is generated from known genetic information". Claim 4 also has been amended by deleting the phrase "consists of" and inserting therefor "comprises". The latter amendment is supported by the specification as filed at p. 7 (lines 11-14) and p. 10 (lines 18-22).

Applicants believe that these amendments overcome the rejection, and reconsideration is requested.

Claims 1-4, 6, 10-11, 17 rejected under 35 U.S.C. 102(a) as being anticipated by Uehling et al (June 1997) – paragraphs 14 and 29-30 of paper number 13.

As required by the Examiner, Applicants hereby make the following remarks of record and incorporate them by reference from the October 19, 1998 Office action in the file history of parent U.S. Patent Application Serial No. 08/923,813 (now U.S. Patent No. 6,099,853). Applicants also enclose three declarations by Drs. Hertelendy, Weiner, and Uehling cited in said file history and make said declarations of record and incorporate them by reference.

In said October 18, 1998 Office action, certain claims:

"...were rejected under 35 U.S.C. §102(a) as being anticipated by Uehling et al., Vaginal Mucosal Immunization for Recurrent Urinary Tract Infection: Phase II Clinical Trial, *Journal of Urology*, 157:2049-2052, 1997. It is the Examiner's position the Uehling et al. made this invention known to others in this country as of May 4, 1996 and also described the invention in a printed publication which was publicly available on May 13, 1997. Applicants respectfully traverse.

As set forth in the Declarations of David T. Uehling, M.D., Zsolt I. Hertelendy, Pharm. D., Ph.D., and Murray Weiner, M.D., which are incorporated into this amendment, Uehling presented to Hertelendy and Weiner a problem he had encountered concerning the intravaginal administration of a urinary tract infection vaccine, SOLCOUROVAC®, a urinary tract infection vaccine manufactured by Solco Basel AG. The problem he encountered was that the liquid vaccine flowed out of the vagina soon after insertion, which severly [sic] limited the amount of time the liquid antigens were in contact with the vaginal mucosal membrane, decreasing the effectiveness of the vaccine.

After Uehling presented such problem to Hertelendy and Weiner, Hertelendy and Weiner invented the suppository-based vaccine delivery system of the subject application to overcome these deficiencies. Uehling was not involved in the formulation, conception, or reduction to practice of the suppositoryt-based [sic] vaccine delivery system of the present invention.

The formulation of the suppository-base vaccine delivery system of the present invention was revealed to Uehling in April 1992 in confidence by Hertelendy and Weiner for the purposes of performing clinical testing on the suppository-base vaccine delivery system. Uehling performed clinical testing only on the suppositories of the present invention as supplied to Uehling by Hertelendy and Weiner. Uehling did not prepare, obtain, or study any vaginal suppository formulations other than those furnished to him by Hertelendy and Weiner.

In May 1996, Uehling gave an oral presentation, referred to in the footnote of Uehling et al., Vaginal Mucosal Immunization for Recurrent Urinary Tract Infection: Phase II Clinical Trial, *Journal of Urology*, 157:2049-2052, 1997, of the results of the clinical testing following treatment of human subjects with the suppository-based vaccine delivery system of the present invention. In such oral presentation, only the results of the clinical testing were disclosed. Uehling did not present, discuss, or disclose the formulation of the suppository-based vaccine delivery system of the present invention.

The formulation of the suppository-based delivery system of the present invention was only publicly disclosed with the permission of Hertelendy and Weiner and was first publicly disclosed in the June 1997 publication of Uehling et al., Vaginal Mucosal

Immunization for Recurrent Urinary Tract Infection: Phase II Clinical Trial, *Journal of Urology*, 157:2049-2052, 1997. Therefore, the suppository-based vaccine delivery system of the present invention was not known or used by others, or patented or described in a printed publication before the invention thereof by Applicants. Accordingly, the withdrawal of the rejection under 35 U.S.C. §102(a) is appropriate and respectfully requested."

Applicants have made the above remarks of record and enclosed copies of the three declarations as required by the Examiner for reliance on an earlier filed declaration. Accordingly, the withdrawal of the rejection under 35 U.S.C. §102(a) is appropriate and respectfully requested.

Claims 1-6, 17 rejected under 35 U.S.C. 103(a) as being unpatentable over Beck et al (U.S. Pat. 4,756,907) in view of Singh (U.S. Pat. 5,858,371 for reasons of record paper number 3, paragraph number 15 – see paragraphs 15 and 31-32 of the 16 and 33-34 of the paper number 13.

Applicants respectfully traverse this rejection, and reconsideration is requested.

Beck et al teaches antibody or antigen containing microparticles for the active or passive immunization of the internal female reproductive organs comprising microparticles of an antigen or antibody incorporated in a matrix material which is biocompatible and biologically degradable, said microparticles capable of being transported after deposition in the vagina by the natural transport mechanism of the internal female reproductive organs across the cervix into the uterus. (Abstract). However, Beck et al offers extensive detail about the complex nature of the transport mechanism, including summary of a reference stating that "...the nature of the particles affects the transport process and that transport is assisted by muscular contractions." (Col. 2, lines 39-41.) Further, "...the refcrence clearly suggests that microcapsules of a size greater than 5 μm will not migrate inward to the internal female reproductive organs." (Col. 2, lines 66-69; emphasis added.) Further details are presented concerning the nature of the mucous of the cervix and the importance of administration of the microparticles during a certain part of the female menstrual cycle. (Col. 5, lines 42-65.)

It is significant that Beck et al teaches away from applicants' invention by emphasizing that the "[t]he size of the microparticles is important insofar as the microparticles must possess sperm surrogate activity such that they can be conveyed by the natural transport mechanism of the reproductive organs upward from the cervix into the uterus and eventually into the fallopian tubes." (Col. 10, lines 26-31.) "If the microparticles are too large, they will cause contractions of the cervix which will expel the microparticles. Microparticles which are too small will not be conveyed upward into the internal reproductive organs. Usually, the microparticles range from 10 to 100 μm, preferably 20 to 70 μm, most preferably 20-60 μm." (Col. 10, lines 31-37; emphasis added.) The critical aspect of these highly specialized teachings is that the microparticles must cross the cervix into the uterus. (Col. 3, lines 29-38.)

Beck et al states that "[c]reams, jellies, foams, or liquids might be used as a suspension medium for microcapsules. Preparations of this type could be placed in the vagina using a loadable syringe or some type of pressurized vaginal inserter." (Col. 15, lines 61-66.) "Vaginal suppositories offer the simplest, most direct method of application." (Col. 16, lines 7-8.) However, there is no teaching or suggestion of applicants' suppository based vaccine system using nucleic acids, proteins or lipids, which are much smaller than the 10 to 100 μm (10,000 to 100,000 nm) size of Beck et al.'s microparticles. Even human cellular chromosomal DNA, condensed at metaphase, has a combined length of only about 200 nm. Biology (5th ed.), Helena Curtis and N. Sue Barnes, editors (Worth Publishers, Inc., NY, NY, 1989), p. 356. Bacterial chromosomal DNA is approximately 1/10th that size or smaller, and viral DNA is much smaller, as is well known to those skilled in the art. Proteins and lipids are smaller still. For example, gram negative bacterial cell walls are made up of macromolecules consisting of lipoproteins, peptidoglycans and lipopolysaccharides (lipid-sugars) that are merely 7 to 8 nm at most. Biology (5th ed.), Helena Curtis and N. Sue Barnes, editors (Worth Publishers, Inc., NY, NY, 1989), p. 432.

Singh et al teaches treatment of anorectal and colonic diseases with a composition comprising flavonoidal constituents. (Abstract.) "The pharmaceutical composition...may also

contain the active agents from other plants and/or from different pharmacological groups such as local anesthetics, vasoconstrictors, protectants, counterirritants, astringents, keratolytics and anticholinergics." (Col. 3, lines 51.55.) "The pharmaceutical compositions...can be dissolved or dispersed in an appropriate base, which can be suppositories, ointments, foams, sprays, medicated pads, capsules and tablets." (Col. 4, lines 41.44.) "The suppository compositions may contain either hydrophobic or hydrophilic base and can include....mixtures of polyethylene glycols of various molecular weights, polyoxyethylene sorbitan fatty acid esters...or a combination of these materials." (Col. 5, lines 3-10.) It is significant that Singh et al teaches only compositions for treatment of anorectal and colonic diseases, and that vaccines are neither taught nor suggested.

Applicants respectfully submit that one skilled in the art would find no reason to combine the highly specialized vaginal immunization teachings of Beck et al with the anorectal and colonic disease treatment teachings of Singh et al that fail totally to teach use of vaccines. Beck et al's compositions must meet limiting criteria because they must cross the cervix into the uterus. Singh et al's compositions are not vaccines but primarily use flavonoids for a completely different purpose, i.e., treatment of anorectal and colonic diseases.

Claims 17 and 19 rejected under 35 U.S.C. 103(a) as being unpatentable over Beck et al (U.S. Pat. 4,756,907) in view of Azria (U.S. Pat. 5,858,371) for reasons of record – see paragraphs 16 and 33-34 of paper number 13.

Applicants traverse this rejection, and reconsideration is requested. Beck et al is discussed fully in the previous section of this response.

Azria et al teaches suppositories comprising a suppository base, a calcitonin and taurocholic acid or a pharmacologically acceptable salt thereof. (Abstract.) Calcitonins are polypeptides that lower calcium levels in the blood and are commonly used in the treatment of Paget's disease, hypercalcemia and osteoporosis. (Col. 1, lines 13-18.) It is significant that

Anria et al teaches only compositions for lowering blood calcium, and that vaccines are neither taught nor suggested.

Applicants respectfully submit that one skilled in the art would find no reason to combine the highly specialized vaginal immunization teachings of Beck et al with the blood calcium lowering teachings of Azria et al that fail totally to mention vaccines. Beck et al's compositions must cross the cervix into the uterus. Azria et al's compositions are not vaccines but rather are a calictonin and taurocholic acid or a pharmaceutically acceptable salt thereof used for a completely different purpose, i.e., lowering blood calcium.

Claim 20 rejected under 35 U.S.C. 103(a) as being unpatentable over Beck et al (U.S. Pat. 4,756,907) in view of Mizuno et al (U.S. 4,462,984) for reasons of record – see paragraphs 17 and 35 -36 of paper number 13.

Applicants traverse this rejection, and reconsideration is requested. Beck et al is discussed fully in the previous section of this response.

Mizuno et al teaches a particular suppository base that provides a melting point of 30°-60°C., excellent moldability and storage stability. (Abstract.) The suppository base composition comprises 5-80% by weight of polyethylene glycol, 5-80% by weight of triglyceride of fatty acid, having a 6-22 carbon atoms and 5-80% by weight of a specifically limited alkylene oxide derivative. (Abstract.) Only vague statements are made regarding "insertion of the suppository into the human body" and "liberation of the drug component." (Col. 3, line 31 and col. 4, lines 1-2.) Mizuno et al neither teaches nor suggests applicants' vaccines for urogenital and anorectal disease.

Applicants respectfully submit that one skilled in the art would find no reason to combine the highly specialized vaginal immunization teachings of Beck et al with the vague suppository and drug teachings of Mizuno et al that totally fail to mention vaccines.

Summary

Applicants submit that the amended claims overcome rejections under 35 U.S.C. 112, first and second paragraphs. Further, Applicants submit that the rejection under 35 U.S.C. 102(a) as being anticipated by Uehling et al has been overcome by (1) making of record in this application certain remarks in the parent application and (2) including copies of three declarations filed in the parent application. Finally, applicants submit that three rejections under 35 U.S.C. 103(a) have been overcome by explanation of the nonobvious nature of applicants' invention.

For these reasons, applicants respectfully request that a timely Notice of Allowance be issued in this case.

Respectfully submitted,

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Attorney Docket No.: 26510-0002

Hertelendy Declaration p. 1 of 3
Serial No. 09/516,078

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF	:	Zsolt I. Hertelendy et al.
FOR	:	VAGINAL SUPPOSITORY FOR UROGENITAL INFECTIONS
SERIAL NO.	:	08/923,813
FILED	:	September 4, 1997
EXAMINER	:	M. Mosher
ART UNIT	:	1643
LAST OFFICE ACTION	:	September 14, 1998
ATTORNEY DOCKET NO.	:	45061-4

Cleveland, Ohio 44114-2378
November 30, 1998

DECLARATION OF ZSOLT I. HERTELENDY, Pharm.D., Ph.D.

I, Zsolt I. Hertelendy, Pharm.D., Ph.D., make the following declaration:

1. In March, 1992, David T. Uehling, M.D., presented to Murray Weiner, M.D., and myself a problem Uehling had encountered concerning the intravaginal administration of a urinary tract infection vaccine, SOLCOUROVAC®, a urinary tract infection vaccine manufactured by Solco Basel AG. The problem Uehling encountered was that the liquid vaccine flowed out of the vagina soon after insertion, which severely limits the amount of time that the liquid antigens are in contact with the mucosal surface of the vagina, decreasing the effectiveness of the vaccine.

Hertelendy Declaration p. 2 of 3

2. After Uehling presented such problem to Weiner and myself, Weiner and I invented the suppository-based vaccine delivery system of the subject application to overcome these deficiencies.

3. Uehling was not involved in the formulation, conception, or reduction to practice of the suppository-based vaccine delivery system of the present invention.

4. The formulation of the suppository-based vaccine delivery system of the present invention was revealed to Uehling in April 1992, in confidence by Weiner and myself for the purposes of performing clinical testing on the suppository-based vaccine delivery system.

5. In May 1996, Uehling gave an oral presentation, referred to in the footnote of Vaginal Mucosal Immunization for Recurrent Urinary Tract Infection: Phase II Clinical Trial, *Journal of Urology*, 157:2049-2052, 1997, of the results of the clinical testing following treatment of human subjects with the suppository-based vaccine delivery system of the present invention. In such oral presentation, only the results of the clinical testing were disclosed.

6. The formulation of the suppository-based vaccine delivery system of the present invention was only publicly disclosed with the permission of Weiner and myself and was first publicly disclosed in the June 1997 publication of Vaginal Mucosal Immunization for Recurrent Urinary Tract Infection: Phase II Clinical Trial, *Journal of Urology*, 157:2049-2052, 1997.

7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like are

Hertelendy Declaration p. 3 of 3

punishable by fine or imprisonment, or both (18 U.S.C. §1001) and may jeopardize the validity of the application or any patents issuing thereon.

Dated: 12-5-98

Zsolt Hertelendy Pharm.D. Ph.D.

Zsolt I. Hertelendy, Pharm.D., Ph.D.

Uehling Declaration p. 1 of 3
Serial No. 08/516,078

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF	:	Zsolt I. Hertelendy et al.
FOR	:	VAGINAL SUPPOSITORY FOR UROGENITAL INFECTIONS
SERIAL NO.	:	08/923,813
FILED	:	September 4, 1997
EXAMINER	:	M. Mosher
ART UNIT	:	1643
LAST OFFICE ACTION	:	September 14, 1998
ATTORNEY DOCKET NO.	:	45061-4

Cleveland, Ohio 44114-2378
October 19, 1998

DECLARATION OF DAVID T. UEHLING, M.D.

I, David T. Uehling, M.D., make the following declaration:

1. In March, 1992, I presented to Zsolt I. Hertelendy, Pharm.D., Ph.D. and Murray Weiner, M.D., the inventors listed in the subject application, a problem I had encountered concerning the intravaginal administration of a urinary tract infections vaccine, SOLCOUROVAC®, a urinary tract infection vaccine manufactured by Solco Basel AG. The problem I encountered was that the liquid vaccine flowed out of the vagina soon after insertion, which severely limits the amount of time that the liquid antigens are in contact with the mucosal surface of the vagina, decreasing the effectiveness of the vaccine.

Uehling Declaration p. 2 of 3

2. I was not involved in the formulation, conception, or reduction to practice of the suppository-based vaccine delivery system of the present invention.

3. The formulation of the suppository-based vaccine delivery system of the present invention was revealed to me in April 1992, in confidence by the inventors for the purposes of performing clinical testing on the suppository-based vaccine delivery system. I performed clinical testing only on the suppositories of the present invention as supplied to me by the inventors. I did not prepare, obtain, or study any vaginal suppository formulations other than those furnished to me by the inventors.

4. In May 1996, I gave an oral presentation, referred to in the footnote of Vaginal Mucosal Immunization for Recurrent Urinary Tract Infection: Phase II Clinical Trial, *Journal of Urology*, 157:2049-2052, 1997, of the results of the clinical testing following treatment of human subjects with the suppository-based vaccine delivery system of the present invention. In such oral presentation, only the results of the clinical testing were disclosed. I did not present, discuss, or disclose the formulation of the suppository-based vaccine delivery system of the present invention.

5. The formulation of the suppository-based vaccine delivery system of the present invention was only publicly disclosed with the permission of the inventors and was first publicly disclosed in the June 1997 publication of Vaginal Mucosal Immunization for Recurrent Urinary Tract Infection: Phase II Clinical Trial, *Journal of Urology*, 157:2049-2052, 1997.

Uehling Declaration pg. 3 of 3

6. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. §1001) and may jeopardize the validity of the application or any patents issuing thereon.

Dated: 11-12-98

David T. Uehling, M.D.

Weiner Declaration p. 1 of 3
Serial No. 09/516,098

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF	:	Zsolt I. Hertelendy et al.
FOR	:	VAGINAL SUPPOSITORY FOR UROGENITAL INFECTIONS
SERIAL NO.	:	08/923,813
FILED	:	September 4, 1997
EXAMINER	:	M. Mosher
ART UNIT	:	1643
LAST OFFICE ACTION	:	September 14, 1998
ATTORNEY DOCKET NO.	:	45061-4

Cleveland, Ohio 44114-2378
November 30, 1998

DECLARATION OF MURRAY WEINER, M.D.

I, Murray Weiner, M.D., make the following declaration:

1. In March, 1992, David T. Uehling, M.D., presented to Zsolt I. Hertelendy, Pharm.D, Ph.D., and myself a problem Uehling had encountered concerning the intravaginal administration of a urinary tract infection vaccine, SOLCOUROVAC®, a urinary tract infection vaccine manufactured by Solco Basel AG. The problem Uehling encountered was that the liquid vaccine flowed out of the vagina soon after insertion, which severely limits the amount of time that the liquid antigens are in contact with the mucosal surface of the vagina, decreasing the effectiveness of the vaccine.

2. After Uehling presented such problem to Hertelendy and myself, Hertelendy and I invented the suppository-based vaccine delivery system of the subject application to overcome these deficiencies.

3. Uehling was not involved in the formulation, conception, or reduction to practice of the suppository-based vaccine delivery system of the present invention.

4. The formulation of the suppository-based vaccine delivery system of the present invention was revealed to Uehling in April 1992, in confidence by Hertelendy and myself for the purposes of performing clinical testing on the suppository-based vaccine delivery system.

5. In May 1996, Uehling gave an oral presentation, referred to in the footnote of Vaginal Mucosal Immunization for Recurrent Urinary Tract Infection: Phase II Clinical Trial, *Journal of Urology*, 157:2049-2052, 1997, of the results of the clinical testing following treatment of human subjects with the suppository-based vaccine delivery system of the present invention. In such oral presentation, only the results of the clinical testing were disclosed.

6. The formulation of the suppository-based vaccine delivery system of the present invention was only publicly disclosed with the permission of Hertelendy and myself and was first publicly disclosed in the June 1997 publication of Vaginal Mucosal Immunization for Recurrent Urinary Tract Infection: Phase II Clinical Trial, *Journal of Urology*, 157:2049-2052, 1997.

7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like are

Weiner Declaration p. 3 of 3

punishable by fine or imprisonment, or both (18 U.S.C. §1001) and may jeopardize the validity of the application or any patents issuing thereon.

Dated: 12/8/98

Murray Weiner, M.D.